Synthesis of *N*-Alkyl-*N*-aryl- and *N*,*N*-Dialkyl-sulfamic Esters by Solid Liquid Phase Transfer Catalytic *N*-Alkylation of the Mono-*N*-substituted Esters

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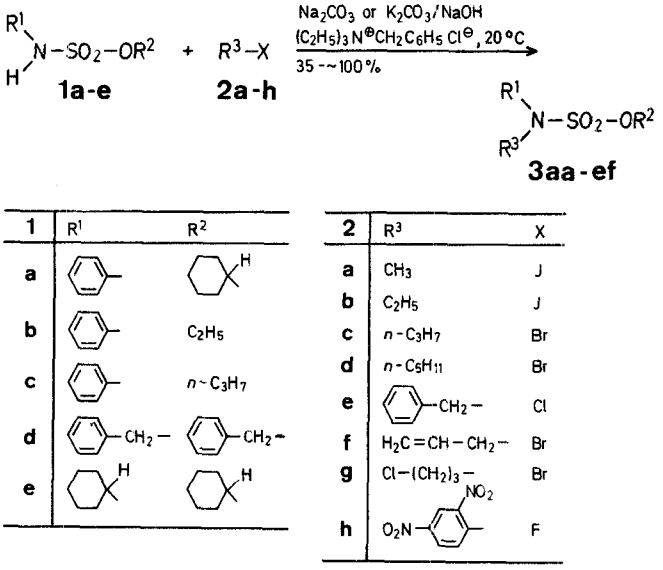
General, high-yield procedures for *N*-alkylation of esters of mono-*N*-substituted sulfamic acids involving reactions at ambient temperatures in the presence of a phase-transfer catalyst and excess alkylating agent have been developed.

In previous work[1] we have developed a high yield, efficient synthesis of arylsulfamic esters **1** (R^1 = aryl). The alkylating ability of these[2,3] and of the *N*-alkyl-*N*-arylsulfamic esters, compounds **3**, has prompted synthesis to study their anti-tumor activity[4-7]. Compounds **3** with $R^2 = R^3$ and R^1 = aryl are synthesised by the use of an external alkylating agent[2], by the reaction of the appropriate arylsulfamic chloride with some simple alcohols (2 equivalents)[1,3], or by the phase-transfer self-alkylation of esters **1** in non-polar solvents[3]. However, the synthesis of **3** when R^1 = aryl and when $R^2 \neq R^3$ is a problem. The lack of reactivity of *N*-aryl-*N*-alkylsulfamyl chlorides with alcohols[1] makes this an impractical route. A Russian group[4] has synthesised a number of the desired type of compounds by the reaction of the appropriate secondary aromatic amines and alkyl chlorosulfates. However, the yields are almost always less than 20% and sometimes substantially less than this. Further, the scope of this synthesis is somewhat limited by the lack of availability of certain alkyl chlorosulfates[8]. The use of aryl fluorosulfates and certain secondary amines does however appear to show greater promise[9]. Lwowski successfully ethylated methyl *N*-phenylsulfamate with ethyl bromide, but self-alkylation of methyl *N*-phenylsulfamate also occurred and the product mixture (from ^{1}H-N.M.R.) contained a 3:1 ratio of desired methyl *N*-ethyl-*N*-phenylsulfamate and methyl *N*-methyl-*N*-phenylsulfamate[2]. In the present work we have developed an efficient, convenient and general synthesis of compounds **3** by *N*-alkylation of esters **1**.

N-Alkylation of organic compounds containing amino proton(s), activated by one or more strongly electron-withdrawing groups, is often conveniently performed under phase-transfer conditions. Reports of such reactions in the literature are many[10], examples include *N*-alkylation of carbamates[11], of carboxamides and sulfonamides[12], and of



1	R^1	R^2
a		
b		C_2H_5
c		n-C_3H_7
d		
e		

2	R^3	X
a	CH_3	J
b	C_2H_5	J
c	n-C_3H_7	Br
d	n-C_5H_{11}	Br
e		Cl
f	$H_2C=CH-CH_2-$	Br
g	$Cl-(CH_2)_3-$	Br
h		F

diphenylphosphinic amide[13]. Sulfamate esters may be viewed as belonging to this general category of compounds.

The present method involves a solid-liquid phase transfer alkylation of esters **1** using a large excess of alkylating agent as solvent. Under these conditions the troublesome self-alkylation reaction of the esters is suppressed and generally high yields of esters **3** are obtained (Table). Fifteen esters of type **3** were synthesised and where comparison could be made our yields were substantially better than those previously reported (see products, **3cb** and **3cc**).

In common with Lwowski we obtained a mixture when we attempted to prepare methyl *N*-ethyl-*N*-phenyl sulfamate by reaction of methyl *N*-phenylsulfamate with ethyl iodide. The Russian group did synthesise this compound but only in 6% yield[4]. We did however obtain in large yield the 'reverse' ester, **3ba** (Table). Three non-aromatic esters, namely, **3da**, **3ea** and **3cf** in which $R^1 \neq R^3$, were also synthesised in good yield. Our method offers an advantage here over that previously used[14] for the synthesis of methyl *N*-ethyl-*N*-methylsulfamate in that the mixed secondary amine is not required as starting material.

Where R^1 = phenyl in compound **1** the acidity of the amino hydrogen is such that deprotonation is easily achieved using sodium carbonate as base. Where R^1 is aliphatic or alicyclic a

Table. *N*-Alkyl-*N*-aryl- and *N*,*N*-Dialkylsulfamic Esters **3** prepared

Substrate	Alkylating agent	Reaction time	Product	Yield [%][a]	m.p. [°C] or b.p. [°C]/torr	Molecular formula[b] or Lit. m.p. [°C] or b.p. [°C]/torr	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[c] δ [ppm]	^{13}C-N.M.R. ($CDCl_3$ or DMSO-d_6/TMS_{int})[d] δ [ppm]
1a	**2a**	15 min	**3aa**	98[g,h]	41–42[e]	$C_{13}H_{19}NO_3S$ (269.3)	1.12–2.16 (m, 10H); 3.40 (s, 3H); 4.58–4.90 (m, 1H); 7.46–7.80 (m, 5H)	22.68, 24.37, 31.64, 39.05, 81.67, 125.66, 127.09, 129.17, 141.64[e]
1a	**2b**	80 min	**3ab**	98	oil	$C_{14}H_{21}NO_3S$ (283.4)	1.16 (t, 3H); 1.28–2.16 (m, 10H); 3.80 (q, 2H); 4.48–4.80 (m, 1H); 7.24–7.56 (m, 5H)	13.25, 22.61, 24.30, 31.58, 46.52, 81.09, 127.74, 129.17, 139.04[e]
1a	**2c**	18 h	**3ac**	92[i,i]	oil	$C_{15}H_{23}NO_3S$ (297.4)	0.92 (t, 3H); 1.12–2.12 (m, 12H); 3.69 (t, 2H); 4.46–4.78 (m, 1H); 7.40–7.68 (m, 5H)	10.92, 21.31, 23.39, 25.08, 32.36, 53.93, 81.61, 128.00, 128.26, 129.30, 139.82[f]

Table. (continued)

Substrate	Alkylating agent	Reaction time	Product	Yield [%][a]	m.p. [°C] or b.p. [°C]/torr	Molecular formula[b] or Lit. m.p. [°C] or b.p. [°C]/torr	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[c] δ [ppm]	^{13}C-N.M.R. ($CDCl_3$ or DMSO-d_6/TMS_{int})[d] δ [ppm]
1a	**2d**	18 h	**3ad**	88[i,j]	oil	$C_{17}H_{27}NO_3S$ (325.5)	0.89 (t, 3H); 1.16–2.16 (m, 16H); 3.72 (t, 3H); 4.48–4.80 (m, 1H); 7.36–7.64 (m, 5H)	13.64, 21.44, 22.61, 24.30, 26.90, 27.68, 31.58, 51.20, 80.96, 127.74, 129.17, 139.30[e]
1a	**2e**	45 min	**3ae**	88	111–113°	$C_{19}H_{23}NO_3S$ (345.45)	1.16–2.08 (m, 10H); 4.46–4.76 (m, 1H); 4.92 (s, 2H); 7.24–7.64 (m, 10H)	22.61, 24.30, 31.58, 54.71, 81.61, 127.48, 128.26, 128.91, 135.93, 138.17[e]
1a	**2f**	40 min	**3af**	98[k]	23–24°	$C_{15}H_{21}NO_3S$ (295.4)	1.16–2.16 (m, 10H); 4.34 (d, 2H); 4.52–4.84 (m, 1H); 5.10–5.40 (m, 2H); 5.76–6.16 (m, 1H); 7.30–7.60 (m, 5H)	22.48, 24.30, 31.45, 54.06, 81.48, 118.77, 127.35, 129.04, 132.68, 139.43[e]
1b	**2a**	15 min	**3ba**	91[l]	24–27°	$C_9H_{13}NO_3S$ (215.3)	1.38 (t, 3H); 3.36 (s, 3H); 4.32 (q, 2H); 7.24–7.60 (m, 5H)	14.55, 39.24, 67.83, 125.92, 127.22, 129.30, 141.51[e]
1b	**2e**	40 min	**3be**	44[k]	68–69°	$C_{15}H_{17}NO_3S$ (291.4)	1.38 (t, 3H); 4.24 (q, 2H); 4.81 (s, 2H); 7.14–7.40 (m, 10H)	14.55, 55.10, 67.83, 127.74, 128.00, 128.26, 129.17, 135.93, 137.17[e]
1c	**2b**	60 min	**3cb**	99 (16)[4]	144–148°/4	156–158°/4.5[4]	0.98 (t, 3H); 1.14 (t, 3H); 1.56–1.92 (m, 2H); 3.74 (q, 2H); 4.12 (t, 2H); 7.20–7.50 (m, 5H)	9.94, 13.58, 22.35, 47.63, 72.38, 128.06, 128.32, 129.36, 139.37[f]
1c	**2c**	15 h	**3cc**	80 (3)[4,m]	155–158°/5	160–163.6°/6[4]	0.82–1.18 (m, 6H); 1.28–1.92 (m, 4H); 3.64 (t, 2H); 4.16 (t, 2H); 7.24–7.52 (m, 5H)	10.07, 10.85, 21.38, 22.48, 54.12, 72.45, 128.06, 128.32, 129.30, 139.63[f]
1c	**2g**	2 h	**3cg**	86[i]	133–136°/0.2	$C_{12}H_{18}ClNO_3S$ (291.8)	0.94 (t, 3H); 1.56–2.20 (m, 4H); 3.51 (t, 2H); 3.80 (t, 2H); 4.08 (t, 2H); 7.28–7.52 (m, 5H)	10.14, 22.48, 31.06, 41.58, 49.77, 72.77, 128.13, 128.39, 129.56, 139.43[f]
1d	**2a**	3 min	**3da**	70[n,o]	54–55°	$C_{15}H_{17}NO_3S$ (291.4)	2.76 (s, 3H); 4.32 (s, 2H); 5.20 (s, 2H); 7.20–7.50 (m, 10H)	34.96, 54.77, 71.86, 128.13, 128.52, 128.71, 129.10, 134.17, 135.34[f]
1e	**2a**	15 min	**3ea**	75[n]	oil	$C_{13}H_{25}NO_3S$ (275.4)	0.80–2.16 (m, 20H); 2.78 (s, 3H); 3.56–3.96 (m, 1H); 4.42–4.76 (m, 1H)	22.61, 24.43, 24.69, 25.21, 29.37, 31.71, 57.70, 79.92[e]
1e	**2h**	6 h	**3eh**	35[i,p]	90–92°	$C_{18}H_{25}N_3O_7S$ (427.8)	0.80–2.32 (m, 20H); 3.76–4.26 (m, 1H); 4.52–4.80 (m, 1H); 7.64–8.68 (m, 3H)	23.39, 24.95, 25.86, 31.71, 32.36, 63.41, 83.30, 120.85, 126.83, 134.50, 136.71, 147.36, 150.09[f]
1e	**2f**	23 h	**3ef**	87[i,q]	oil	$C_{15}H_{27}NO_3S$ (301.45)	0.84–2.48 (m, 20H); 3.44–3.72 (m, 1H); 3.81 (d, 2H); 4.44–4.72 (m, 1H); 5.04–5.44 (m, 2H); 5.68–6.12 (m, 1H)	23.39, 25.08, 25.34, 25.99, 31.32, 32.36, 35.74, 47.43, 59.26, 80.44, 116.95, 135.67[f]

[a] Isolated yield of analytically pure product. Literature yield is given in brackets. All products showed ν_{SO_2}-asymmetric and symmetric stretching vibrations in the ranges 1350–1380 and 1166–1184 cm^{-1} respectively in their I.R. spectra (neat or Nujol null. measured on a Perkin Elmer 983G spectrophotometer.

[b] Satisfactory microanalyses obtained: C ± 0.37, H ± 0.33, N ± 0.41. Exceptions: **3ac**, +0.46; **3ad**, −1.8; **3cc**, +0.45; **3ca**, +0.5.

[c] Recorded on a Jeol JNM-100 spectrometer.

[d] Recorded on a Jeol FX-60 spectrometer.

[e] Measured in DMSO-d_6.

[f] Measured in $CDCl_3$.

[g] Without the catalyst a yield of 36% was obtained in 15 h.

[h] When reaction was carried out in benzene at 18°C using a twofold excess of methyl iodide a yield of 81% was obtained in 24 h.

[i] Product purified by flash chromatography using petroleum ether (40–60°C) / ethyl acetate (8:1 V/V).

[j] Formation of an unreactive paste avoided by using 2 g anhydrous sodium carbonate.

[k] The last races of the alkylating agent, R^3-X were removed using the 'cold finger' technique.

[l] This compound formed as a solid glass like material.

[m] A 45% yield was obtained after 4 h using a twofold excess of *n*-propyl bromide in refluxing chloroform.

[n] No reaction observed (T.L.C. and ^{1}H-N.M.R.) when sodium carbonate was used as base.

[o] Extensive side product formation occurred after reaction was left on for more than 3 min.

[p] The conditions were not optimised.

[q] Using calcium hydroxide as base and 10% mol benzyltriethylammonium chloride.

stronger base is required and we have found both Zwierzak's sodum hydroxide/potassium carbonate mixture[15] and calcium hydroxide to be suitable (though with calcium hydroxide reaction time is longer).

Arylation of **1a** using 2,4-dinitrofluorobenzene gave a high yield of phenyl 2,4-dinitrophenylamine rather than anticipated **3ah**. Strong electron-withdrawal in **3ah** renders it unstable and it decomposes to the secondary amine. Finally, it has been shown that compound **3** can also give rise to secondary amines by acid hydrolysis. Thus, **3be** gave 60% of *N*-phenylbenzylamine. This yield of secondary amine is comparable to those previously reported[4]. Analogous N-S cleavage reactions of sulfonamides have been reviewed[16].

The alkylating agents were commercially available and were used as obtained. Other solvents were generally distilled and dried prior to use. *N*-Methyl-*N*-phenyl-, -phenyl-, -cyclohexyl-, and -benzylsulfamic chlorides were prepared as reported previously[1,17,18,19]. *N*-*n*-Butyl-*N*-ethylsulfamic chloride was prepared by the method of Klock and Leschinsky[17], as modified[19]. The latter distilled at 63–65 °C/0.11 torr giving a 76% yield of a clear liquid which was not analytically pure. However, its I.R., ^{1}H- and ^{13}C-N.M.R. spectra indicated it to be sufficiently pure for further reaction. Esters **1a–f** have all been prepared previously (% yield in brackets): **1a**[1] (48), **1b**[1] (80) and [2] (65), **1c**[3] (not given), **1d**[20] (not given) and **1e**[21] (32). We were in some cases able to improve yields as follows: **1a** (74), **1b** (54), **1c** (71), **1d** (41) and **1e** (64). This involved a slightly modified procedure to that previously reported[1].

Sulfamic Esters **1**; *Modified Procedure:* A suspension of the appropriate alcohol (0.02 mol), anhydrous sodium carbonate (8 g), and tetra-*n*-butylammonium bromide (0.008 mol) is stirred in dry benzene (8 ml) at ambient temperature for ~ 30 min. Sulfamic chloride (0.02 mol) in dry benzene (7 ml) is added dropwise over 40 min and stirring is maintained for a further 30–60 min. Each product ester **1** is purified by flash chromotography using as eluent the appropriate[22] ratio of petroleum ether (40–60 °C) to ethyl acetate. The purity of the esters **1a–e** is confirmed by I.R., ^{1}H-, and ^{13}C-N.M.R. spectroscopy, and by microanalysis.

N-Alkyl-N-aryl- and N,N-Dialkylsulfamic Esters 3; General Procedures:

N-*Alkyl*-N-*arylsulfamic Esters:* Compound **1** (2 mmol), anhydrous sodium carbonate (3.2 g), benzyltriethylammonium chloride (371 mg, 2 mmol), and the alkylating agent (7 ml) are vigorously stirred in a sealed flask at ambient temperature. The reaction is monitored by T.L.C. (*n*-hexane/ethyl acetate, 3/1). Upon completion of reaction, *n*-hexane (~ 35 ml) is added and the mixture stirred and filtered. Removal of solvent from the filtrate at reduced pressure (initially ~ 20 torr and finally 1.0 torr) at 40 °C affords the crude product as a clear viscous oil. Unreacted alkylating agent is generally recovered in good yield. In the case of a solid product, the oil crystallised upon refrigeration. The solids are pulverised and placed for ~ 12 h. in a vacuum dessicator. The obtained products are generally spectroscopically (I.R., ^{1}H-, and ^{13}C-N.M.R.) and analytically pure. Impure liquid products are purified using flash chromatography and solids are purified by dissolving in minimum cold dichloromethane/*n*-hexane (~ 1/3) filtering and allowing the filtrate to stand for a few hours, first at room temperature and finally at − 20 °C. The resultant solids are filtered and dried in a vacuum dessicator over calcium chloride.

Cyclohexyl. N-*(2,4-dinitrofluoro)-phenyl*-N-*cyclohexylsulfamate* (**3eh**): A mixture of **1e** (261 mg, 1 mmol), benzyltriethylammonium chloride (18.6 mg, 0.1 mmol), finely powdered sodium hydroxide (0.2 g), anhydrous potassium carbonate (1 g), 2,4-dinitrofluorobenzene (186 mg, 1 mmol), and benzene (4 ml) is stirred at ambient temperature for 6 h. The reaction is monitored by T.L.C. (*n*-hexane/ethyl acetate/chloroform, 16/3/8) and the crude product is purified by flash chromatography as above. The resultant yellow oil solidifies upon refrigeration and is recrystallised from *n*-hexane/dichloromethane (6/1).

N,N-Dialkysulfamic Esters **3da, 3ea, 3ef**: A mixture of compound **1d** or **1e** (2 mmol), benzyltriethylammoniumchloride (371 mg, 2 mmol), finely powdered sodium hydroxide (0.8 g), anhydrous potassium carbonate (2 g), and the alkylating agent **2a** or **2f** (7 ml) are vigorously stirred at ambient temperature. Reaction monitored by T.L.C. (*n*-hexane/ethyl acetate, 4/1; iodine detection where applicable). Work-up as above yields spectroscopically (I.R., ^{1}H-, and ^{13}C- N.M.R.) and analytically pure products.

Arylation of 1a; Phenyl-2,4-dinitrophenylamine:

A mixture of **1a** (261 mg, 1 mmol), benzyltriethylammonium chloride (186 mg, 1 mmol), anhydrous sodium carbonate (1.5 g), and 2,4-dinitrofluorobenzene (186 mg, 1 mmol) in dry benzene (6 ml) are vigorously stirred at ambient temperature. The reaction is monitored by T.L.C. (*n*-hexane/ethyl acetate/chloroform, 16/3/6). At the completion of the reaction ether (20 ml) is added and the mixture stirred and filtered. Removal of solvent from the filtrate affords the crude material as an oil. Flash chromatography using the same system as above for elution gives phenyl 2,4-dinitrophenylamine: yield: 230 mg (89%); m.p. 156–157 °C (Lit.[23], m.p. 157 °C).

Cleavage of 3be to give N-Phenylbenzylamine:

A mixture of **3be** (0.2 g, 0.68 mmol) in concentrated hydrochloric acid (10 ml) and 95% ethyl alcohol (5 ml) is refluxed for 30 min. The solution is then cooled and extracted with *n*-hexane (4 ml). Slow draining of the aqueous layer into a cooled solution of ~ 20% potassium hydroxide (20 ml) followed by refrigeration affords *N*-phenylbenzylamine. This is filtered, washed with cold water, and dried; yield: 0.075 g (60%); m.p. 31–34 °C (Lit.[23], m.p. 37–38 °C).

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